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THE SPASMOLYTIC SUBSTANCE THIPHEN

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A new spasmolytic was synthesized at the All-Union Chemicopharmaceutical Scientific Research Institute imeni S. Ordzhonikidze (VNIKhFI) and released under the name of thiphen /tifen/. Thiphen, the hydrochloride of the diethylaminoethylester of diphenylthioacetic acid, has the following formula:

$$CCOSCH_2CH_2N(C_2H_5)_2 \cdot HCl$$

Thiphen is similar in constitution to spasmolytin (hydrochloride of diethylaminoethylester of diphenylacetic acid), which was synthesized earlier at the same institute. Spasmolytin is known in the literature as trasentin.

Thiphen is a white crystalline powder which has a bitter taste and is soluble in water. Its melting point is 122-4°C.

A pharmacological investigation which we carried out showed that thiphen has spasmolytic properties which exceed those of trasentin and papaverine. Preliminary experiments carried out on a section of rabbit intestine demonstrated that thiphen is effective in relaxing muscle tonus at concentrations beginning with 1:5 million, and that its action is 3-4 times stronger than that of papaverine and 2-3 times stronger than that of trasentin. Muscle spasm produced in a section of guinea pig intestine by barium chloride, acetylcholine, carbocholine /carbamylcholine/, or histamine was easily removed by adding thiphen to a beaker containing the isolated organ. The spasmolytic effect of thiphen was also tested on live cats and dogs in which spasms were produced by the intravenous injection of carbocholine or application of acetylcholine.

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Spasms of the intestine in cats and of the bladder in dogs were eliminated by administration of thiphen. At the same time, changes in the blood circulation produced by carbocholine were reversed.

As far as vasodilatory effects are concerned, trasentin is about equivalent to papaverine, while thiphen is considerably more effective than papaverine. With respect to the nature of its action, thiphen resembles papaverine. However, it also exhibits properties similar to those of atropine, as can be seen from its ability to counteract the effects of acetylcholine and carbocholine. The fact that the drug exerts an action of the atropine type is confirmed by the observation that it prevents the transmission of an impulse along the system of the vagus. The toxicity of thiphen is low; on subcutaneous injection into mice, it was found to be only about one half as toxic as papaverine. Animal experiments demonstrated that the effect of the new spasmolytic on respiration is rather irregular. Another pharmacological property of thiphen is its local anesthetic action.

Clinically thiphen was found to be beneficial in stenocardia, angiospastic headaches, cholecystitis, cases of gastric ulcers, and bronchial asthma. In Professor B. Ye. Votchal's clinic, a distinct lowering of the tonus of bronchial muscles with improvement of bronchial permeability was established by the pneumotachometric method after application of thiphen. Papaverine, eupaverine, and perparin do not have any such effect.

No undesirable side effects were observed after the administration of thiphen, even in cases when the treatment was continued for 35 days. Patients who received the drug in the form of powder rather than tablets occasionally complained about the disagreeable taste and the feeling of numbness in the mouth which resulted from the local anesthetic action of the drug.

The Pharmacological Committee of the Scientific Medical Council of the Ministry of Public Health USSR has permitted the use of thiphen in general medical practice.

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